Chapter 3

PATHOGENESIS

1) The Digestive Tract
2) The Body's Defense System
3) High-Risk Populations
4) Infective or Toxic Dose

PATHOGENESIS

Introduction
Ingested pathogens, transmitted from contaminated foods, enter the body by way of the gastrointestinal (GI) tract. The body has defenses to fight these pathogens, but an overwhelming dose of pathogens or a weakened resistance can lead to illness. Certain populations, for example, the very young, the elderly, and some immunocompromised persons, are at higher risk for foodborne disease and for serious complications of foodborne disease. The severity of illness may be different among people eating the same contaminated food. The variability in illness severity is due to several factors including: the virulence of the pathogen, the health status of the host, and the concentration of the pathogen. The minimum dose of pathogens necessary to cause illness varies from organism to organism and host to host.

1) The Digestive Tract

Food digestion begins in the mouth, where the food is mixed with enzyme-containing saliva, and then continues in the stomach, where other acid and enzymes in the gastric juice are added. The large molecules of proteins, fats, and carbohydrates cannot be used until they move to the small intestine where they are digested into smaller molecules by enzymes. Normal intestinal bacteria are present in large quantities and aid in digestion.

The surface layer of the small intestine consists of a lining called the epithelium that mediates exchanges between the partially-digested food and the deeper tissue layers containing blood, lymph vessels, glands and nerves. The smaller molecules are absorbed across this lining into the blood and the lymph. Hence, the molecules gain entry into the body and are used for energy and other bodily requirements. The large intestine has comparatively little digestive function. It mainly absorbs water and electrolytes from the digested food. It then expels the resulting waste products as feces, which contain undigested material (fiber), but is mostly normal bacteria by weight.

The digestive tract is under frequent attack, and serves as the main line of defense against the actions of potential foodborne pathogenic microorganisms. Illness results when the number of microorganisms or the concentration of their toxins overwhelms the body's threshold point. Most foodborne exposures are mild, the body successfully fights off the microorganisms, and the person never experiences any symptoms of illness. Or, a person

may experience mild abdominal symptoms, or perhaps more severe symptoms, without realizing that the cause was foodborne.

The threshold point for illness differs from person to person and is affected by various factors described in the following sections. For pathogens that cause infections, the threshold point is termed the **infective dose**; for pathogens that cause intoxications, it is termed the **toxic dose**. The frequency and severity of illness usually increases as the dose consumed exceeds this threshold. This is termed an illness or attack rate dose-response relationship. (See Table 3.3 at the end of this chapter for the infective and toxic dose of various microorganisms.)

2) The Body's Defense System

The human body possesses a wide variety of defense mechanisms for counteracting foodborne pathogens. The components of the GI defense system include:

- stomach acid pH,
- GI tract immune system,
- intestinal flora, and
- bile acids and digestive enzymes.

A. Stomach pH

The gastric fluid present in the stomach is quite acidic, with a pH of about 2. Many bacteria that enter the stomach are killed in such an environment. The pH indicates the degree of acidity or alkalinity of a substance. A neutral substance, such as water, has a pH of 7. Acids have a pH less than 7 and bases have a pH ranging from 7 to 14.

The acidity of the stomach can reduce or eliminate pathogenic microorganisms or toxins before they can reach the small intestine, where most absorption occurs. Anything decreasing stomach acidity (resulting in increased pH) can potentially protect many pathogens and toxins and increase their chance of reaching the small intestine rendering the person more susceptible to illness. Such factors include:

- the buffering capacity of food (e.g., the components of milk decrease acidity),
- the consumption of antacids (these are buffering agents and decrease acidity),
- the use of certain drugs, acid blockers (e.g., cimetidine and ranitidine for treatment of ulcers inhibit the secretions of stomach acids),
- partial or total gastrectomies (these are associated with decreased acidity).

Salmonella is a good example of a bacterium that benefits from the buffering capacity of foods. Relatively large numbers of *Salmonella* bacteria are normally required to cause illness in healthy adults. However, infection can occur with lower doses from foods that protect *Salmonellae* from the acidity of the stomach (e.g., milk). The same applies to

Campylobacter species if the organism is consumed with milk or other foods that neutralize stomach acidity.

Clostridium botulinum has an effective way to cause illness while being protected against the acidity of the stomach. When growing in contaminated foods, it makes a toxin consisting of two parts (toxic and nontoxic). The toxic part induces the illness but is easily altered by stomach acidity. The nontoxic portion serves to protect the toxic part during passage through the stomach. After passage to the small intestine, the toxin is released by intestinal enzymes, thus causing illness.

B. The GI Tract Immune System

The GI tract has its own immune system. It is related to, but distinct from, the overall immune system. The GI tract immune system helps to keep the body healthy by reducing absorption of some large molecules or reducing colonization or invasion of the epithelium by pathogens. It does all of this without affecting normal bacterial flora.

Large particles, such as toxins, are immobilized within the epithelium. Certain enzymes can then attack the immobilized form. Another way in which the intestines minimize entry of particles into the body is by breaking down particles that attach to the bowel wall. The intestinal wall also contains lymphocytes and antibody producing cells that fight infection. Generally only organisms that can attach to the intestinal lining cause problems. Otherwise organisms are swept out by the motility of the GI tract.

Although the intestinal immune system is well designed to handle many invading molecules and pathogens, certain ones are difficult to control. Some pathogenic microorganisms can change their outside surfaces so that they are not recognized or are considered harmless. They are therefore not attacked or eliminated by the host and can then cause illness.

Persons who have been exposed to certain pathogens or toxins may develop partial or total immunity to later exposures to the same pathogen/toxin. The immunity results from a specific immune reaction and greatly increases the infective or toxic dose required to cause subsequent illness. For example, hepatitis A antibodies appear early in the course of infection, remain detectable for the person's lifetime and indicate lifelong immunity. Subsequent exposure to hepatitis A will not result in illness.

C. The Intestinal Flora

More than 400 species of bacteria (also called normal flora) live in the adult human GI tract. These flora can provide resistance to colonization by some pathogenic microorganisms. Animal studies indicate that colonization resistance exerted by the normal flora increases throughout adulthood. In the healthy individual, host tissues and the normal GI flora operate in harmony.

Most foodborne pathogens are not normal inhabitants of the intestines. Exceptions include certain strains of *Clostridium perfringens* and *Escherichia coli*, which are normal inhabitants of the intestinal tract, but are not virulent strains causing disease in the healthy individual.

To cause illness, foodborne pathogens must be able to compete successfully against the normal flora. They must be able to either colonize the epithelial surface or hide from the GI immune system. Some pathogens produce attachment factors which enable them to colonize the intestinal walls. Others produce enzymes, toxins, or other compounds altering permeability or damaging epithelial cells allowing pathogens to invade. A few examples to help illustrate this are described below.

Shigella are localized in the intestinal cells where they remain attached to, or multiply within these cells. They cause a severe local inflammatory response which results in a bloody, mucopurulent diarrhea. Unlike S*higella*, *Vibrio cholerae* do not penetrate the epithelial layer, but remain adhered to it. The pathogen produces severe diarrhea, resulting from the secretion of a toxin that affects the underlying cells.

Manifestations of some foodborne diseases are not restricted to the GI tract. For example, *Salmonella typhi* (*S. typhi*) can move through the intestinal wall penetrating the epithelial cells. Following inflammation in the small intestine, the organisms may invade the regional lymph nodes. From the lymphatic system, they may enter the blood and infect various organs and tissues, including the liver, kidneys, spleen, bone marrow, gall bladder and even the heart. Symptoms of *S. typhi* infection include headache, loss of appetite, abdominal pain, weakness and a continued fever. Hepatitis A is an example of a virus that moves beyond the GI tract into the liver. Other microorganisms that play an etiologic role in illness beyond the GI tract include: *E. coli* O157:H7 (hemolytic uremic syndrome), *Campylobacter jejuni* (Guillain-Barré syndrome) and *Listeria monocytogenes* (fetal morbidity and meningitis).

D. Bile Acids and Digestive Enzymes

Bile acids are produced in the liver and assist in the digestion and absorption of fat. They inhibit the growth of many pathogenic microorganisms. They are thought to be partly responsible for preventing *Clostridium botulinum* from producing toxin in the intestinal tract of adults. However, other enteric microorganisms such as *Escherichia*, *Salmonella*, and *Shigella* are not affected by bile acids.

Digestive enzymes are active throughout the GI tract. As mentioned in the preceding sections of this chapter, many may inhibit or inactivate a variety of microorganisms. For example, lysozyme in saliva kill and digest microbes. In some cases, however, as with botulinum toxin, GI enzymes actually play a role in activating a toxin.

E. Treatment

While antibiotic therapy is sometimes useful in treating foodborne illness, it can sometimes be ineffective or actually make the condition worse. Antibiotics can prevent the growth of normal flora. In the absence of normal flora, pathogenic bacteria may become established. Normally, such organisms do not flourish in the intestines because they cannot compete with the normal flora. But with the normal flora eliminated from antibiotic use, they can take over.

Furthermore, oral antibiotics can facilitate intestinal colonization of certain foodborne pathogens and prolong carriage. For example, antibiotic therapy is usually not indicated for those patients with uncomplicated gastroenteritis caused by non-typhi *Salmonella* species. Antibiotic therapy can prolong the excretion of *Salmonella* organisms into feces. Treatment is indicated however for those patients with invasive disease or an increased risk of invasive disease, such as infants younger than 3 months of age and immunocompromised individuals.

There does not appear to be a role of antibiotic treatment for patients with *E. coli* O157:H7. Some studies have demonstrated that antibiotics (such as trimethoprim sulfamethoxazole) have no effect on the progression of symptoms, fecal pathogen excretion or progression to HUS. Other analyses have demonstrated that trimethoprim sulfamethoxazole can increase the chances of progression to HUS. The data are insufficient to provide an answer at this time, and further studies need to be done.

Overall, antibiotic therapy should be used with care, especially if the pathogen is resistant and the normal flora is sensitive to the antibiotic.

3) High-Risk Populations

Certain populations of people are predisposed to prolonged, more frequent, and often more severe illness. As the population of the U.S. ages, an increasing percentage of the population is becoming more susceptible to foodborne pathogens (see Table 3.1). Elderly individuals undergo a decrease in immune function and are more susceptible to microbial infections and to the complications of diarrheal disease (e.g., dehydration). Those older than 65 years account for approximately 10% of the U.S. population, and this number is growing by about 1 million per year.

Individuals immunocompromised as a result of transplant operations, chemotherapy, or AIDS are also potentially at higher risk for certain foodborne illnesses. Immunocompromised individuals may also be infected by lower infective or toxic doses of pathogenic microorganisms than healthy individuals.

Listeria and *Salmonella* are much more pathogenic in immunocompromised individuals. The risk of infection with *Listeria* is estimated to be 100 to 300 times higher in patients with AIDS. For these individuals, the illness carries a mortality rate of 23 percent. The

risk of infection with *Salmonella* is 20 times higher for these same individuals, with septicemia six times more likely to develop as a complication of infection. The number of U.S. transplant patients requiring continued immunosuppressive therapy is increasing each year; with the number of heart, kidney, liver, and pancreas transplants increasing by as much as 50% annually. Immunosuppressive therapy can reduce the ability of the body's immune system to fight off infection from pathogens.

TABLE 3.1 Populations Sensitive to Foodborne Disease in the United States

Population Category	Individuals	Year
Pregnant women	6,484,000	1992
Children under 5 years	19,286,000	1996
Elderly (over 65)	33,200,000	1994
Cancer patients	1,208,000	1994
Organ transplant procedures	17,331	1994
AIDS patients	66,816	1996

Source: U.S. Department of Commerce, 1996; U.S. Department of Health and Human Services, 1996.

Other factors may also increase an individual's risk for foodborne illness. Pregnancy puts a woman's fetus at risk for infections with *Listeria monocytogenes* or *Toxoplasma gondii*. Each of these organisms may cause abortion, stillbirth or fetal abnormality. Patients with sickle cell disease are at high risk of invasive *Salmonella* infection. Additionally, hospitalized persons are at increased risk for microbial infection. Nearly one-third of all hospitalized patients are treated with antibiotics. As mentioned in Section 2 of this chapter, antibiotic treatment alters the normal flora leaving one more vulnerable to foodborne illness.

In total, more than 30 million individuals in the United States are likely to be at high risk for foodborne illness. These and other factors discussed in this chapter are presented in Table 3.2 at the end of the chapter.

4) Infective or Toxic Dose

The minimum infective or toxic dose of microorganisms needed to cause illness for an individual is difficult to determine because of all the variables described. Not everyone exposed to a contaminated food will become clinically ill. Doses necessary to cause illness can range from one to hundreds to millions of microorganisms.

Predictions have been made to determine the number of pathogens needed to cause illness. These predictions were developed from human feeding studies and are based on probability models. One study by Rose and Sobsey (1993) estimates that individuals consuming 60 grams of raw shellfish from approved waters in the United States may have on average a 1 in 100 chance of becoming infected with an enteric virus. When the

rotavirus probability model is used, which represents a more infectious virus, the risk increases to 5 in 10. These predictions can help explain why outbreaks continue to occur.

These studies should be interpreted with caution because of the limitations of sampling and laboratory methodology. The feeding trials are usually done with healthy young men who may report mild or no illness, whereas in an actual outbreak, lower levels of pathogens may cause illness due to the variations of people involved. Also, the food may have a significant effect on infectivity, for example, certain foods may be especially efficient vehicles for transmission of infectious or toxic agents in that they enhance the probability of infection or illness (e.g., milk).

Additionally, pathogens that cause illness differ greatly among types, genera, species and strains. Not all microorganisms sharing the same genus and species name (e.g., *Escherichia* is the genus and *coli* is the species) are identical, and they may differ greatly in their infectiousness. In fact, some may not be capable of causing human illness, while others are quite hazardous. Additionally, smaller numbers of pathogens can more easily cause illness in a person who is at higher risk than in one who is not.

The probability of infection and subsequent illness is a function of:

- **the vulnerability of the host (e.g., age, immune resistance),**
- **the number of units of the infectious agent ingested with food (e.g., viral particles, bacterial cells, parasitic cysts), and**
- **the virulence or pathogenicity of the agent.**

Table 3.3 at the end of the chapter presents what is currently known of the infectivity/toxigenicity of the more common agents. This information has been drawn from human feeding studies as well as from foodborne illness outbreaks.

Conclusion

Chapters 4-8 of this reference manual cover the sequential events in the investigation of foodborne illness. While chapters 1-3 consist of background or textual information, the following chapters contain more of the “how to” or “hands on” material. Each chapter provides information on a specific part of an investigation. Keep in mind that these events do not necessarily happen in the order that the material is printed. Many events happen simultaneously; note the various references to other chapters and sections as you go along.

References

Acheson, D. and Keusch, G. Which Shiga Toxin-Producing Types of *E. coli* Are Important? *ASM News*. 1996; Vol. 62, No. 6.

American Academy of Pediatrics. *1994 Red Book: Report of the Committee on Infectious Diseases*. Illinois: American Academy of Pediatrics, 1994.

Blaser, M. How Safe Is Our Food? *The New England Journal Of Medicine.* 1996; Vol. 334, No. 20, 1324-1325.

Brock, T. and Brock, K. *Basic Microbiology With Applications*, *Second Edition*. New Jersey: Prentice-Hall, Inc. 1978.

CAST (Council For Agriculture Science And Technology). *Foodborne Pathogens, Risks and Consequences. Task Force Report*. No. 122, September 1994.

CDC. *HIV/AIDS Surveillance Report, Year-end edition*, December 1996, Vol. 7, No. 2.

CDC. Outbreaks of *Escherichia coli* O157:H7 Infection and Cryptosporidiosis Associated with Drinking Unpasteurized Apple Cider - Connecticut and New York, October 1996. *MMWR* 1997; Vol. 6, No. 10.

CDC. Viral Agents of Gastroenteritis. *MMWR* 1990;Vol. 39, No. RR-5. Department of Health Working Group. *Management of Outbreaks Of Foodborne Illness*. Department of Health, England, 1994.

Frenkel, J.K. Toxoplasma In And Around Us. *BioScience* 1973; 23:343-352.

Mandell, G. et al. *Douglas and Bennett's Principles and Practices of Infectious Diseases*. New York: Churchill Livingstone, 1995.

Mims, C.A. *The Pathogenesis of Infectious Diseases*. London: Academic Press, Inc. 1987.

National Foundation For Infectious Diseases. Clinical Approach to the Management of Acute Diarrhea. *Infectious Diseases, Clinical Updates*. 1994; Volume II, Issue 2.

Pickering, L.K. et al. Hemolytic Uremic Syndrome and Enterohemorrhagic *Escherichia coli*. *The Pediatric Infectious Disease Journal*. 1994; Vol. 13, No. 6.

Rose, J.B. and Sobsey, M.D. Quantitative risk assessment of viral contamination of shellfish and coastal waters. *Journal of Food Protection* 1993; 56:1043-1050.

Southwick, F. and Purich, D. Intracellular Pathogenesis Of Listeriosis. *The New England Journal Of Medicine*. 1996; Vol. 334, No. 12, 770-776.

Tarr, P.I. *Escherichia coli* O157:H7: Clinical, Diagnostic, and Epidemiological Aspects of Human Infection. *Clinical Infectious Diseases* 1995:20.

U.S. Department of Commerce. 1996. *Statistical Abstracts of the United States*. National Databook. Bureau of the Census, U.S. Department of Commerce, Washington, D.C.

Volk, W. et al. *Essentials of Medical Microbiology*, Fourth Edition. Philadelphia: J.B. Lippincott Company, 1991.

TABLE 3.2 Factors Increasing the Risk or Severity of Foodborne Illness

FACTORS	REASONS
Microbial Factors:	
Type and strain of pathogen ingested	Some pathogens and strains more virulent than others
Quantity of pathogens ingested	Higher numbers ingested may increase severity of illness and/or shorten onset time
Host Factors:	
Age less than 5 years	Lack of developed immune systems, smaller infective dose-by-weight required
Age greater than 50 or 60 years (depending on pathogen)	Immune system failing, weakened by chronic ailments, occurring as early as 50 to 60 years of age
Pregnancy	Altered immunity during pregnancy
Hospitalized persons	Immune systems weakened by other diseases or at risk of exposure to antibiotic-resistant strains
Concomitant infections	Overloaded or damaged immune systems
Consumption of antibiotics	Alteration of normal intestinal microflora
Excessive iron in blood	Iron in blood serving as nutrient for some organisms
Reduced liver/kidney function (alcoholism)	Reduced digestion capabilities, altered blood-iron concentrations
Possession of certain human antigenic determinants duplicated or easily mimicked by microorganisms	Predisposition to chronic illness (sequelae)
Surgical removal of portions of stomach or intestines	Reduction in normal defense systems against infection
Immunocompromised individuals including those on chemotherapy or radiation therapy; recipients of organ transplants taking immunocompromising drugs; persons with leukemia, AIDS, or other illnesses	Immune system inadequate to prevent infection
Stress	Body metabolism changes allowing easier establishment of pathogens, or lower dose of toxin required for illness
Poor hygiene	Increased likelihood of ingestion of pathogens
Diet related factors:	
Nutritional deficiencies either through poor absorption of food (mostly ill or elderly persons) or unavailability of adequate food supply (starving persons)	Inadequate strength to build up resistance and/or consumption of poor-quality food ingredients, which may contain pathogens
Consumption of antacids	Increased pH of stomach
Consumption of large volume of liquids including water	Dilution of acids in the stomach and rapid transit through the stomach
Ingestion of fatty foods (such as chocolate, cheese, hamburger) containing pathogens	Protection of pathogens by the fat against stomach acids
Other factors:	
Geographic location	Likelihood of exposure to endemic virulent strains, limited food and water supply, varied distribution of organisms in water and soil

Source: CAST, Foodborne Pathogens Risks and Consequences, 1994. Used with permission.

TABLE 3.3 Infectivity or Toxigenicity of Various Microorganisms

AGENT	INFECTIVITY/TOXIGENICITY
Bacillus cereus	Symptoms arise after ingestion of food containing large numbers of toxigenic bacteria (> 10^5/g), or preformed toxin.
Campylobacter jejuni	As few as 100 organisms can cause illness if consumed with milk or other foods that may neutralize gastric acidity.
Clostridium botulinum	The toxin is potentially lethal at very low doses.
Clostridium perfringens	Usually >10^6 microorganisms are required to cause illness.
Cryptosporidium species	High infectivity, approximately 100-150 organisms can cause illness.
E. coli O157:H7	Relatively high toxigenicity as <1000 bacteria can cause illness.
Giardia lamblia	As few as 25-100 cysts can cause illness.
Hepatitis A	High infectivity, as approximately 10-100 particles of virus can cause illness.
Listeria monocytogenes	Not highly pathogenic for healthy adults outside high-risk groups.
Salmonella species (excluding *S. typhi* and *S. paratyphi*)	Normally, relatively large numbers of bacteria (10^5) required to cause illness in healthy adults, but vulnerable groups can be infected by lower numbers. Infection can occur from relatively low doses, particularly in foods that protect salmonellae from the acidity of the stomach.
Salmonella typhi *Salmonella paratyphi*	Variable infectivity. 10^5-10^9 bacteria may be required to cause illness, depending on the strain and host susceptibility. As few as 10 to 100 *S. typhi* have caused illness.
Shigella species	Small numbers of bacteria (10-100) have caused illness in volunteers.
Staphylococcus aureus enterotoxin	Illness can occur in the absence of live cells; toxin may have been produced, and the organisms may die out. Sufficient toxin to cause illness may be produced if bacterial numbers reach 10^5 to 10^6.
Vibrio cholerae serotype 01 and non 01 strains	10^6 organisms cause illness. If given with alkali to neutralize stomach acidity as few as 100-1000 can cause disease.
Vibrio parahaemolyticus	Relatively low infectivity - at least 10^5 to 10^7 organisms of virulent strain may be required to cause illness.
Viruses	Relatively high infectivity. For example, the infective dose of rotavirus in a child can be as few as 10 particles.
Yersinia enterocolitica	Relatively low infectivity. Larger numbers are required to cause illness.

Data taken from: Mandell, G. et al, 1995, and Department of Health Working Group, England, 1994.